In the United States Patent and Trademark Office

In Re Chisari et al.	
Serial No.:	08/854,825
Filing Date:	May 12, 1997
For:	HEPATITIS C VIRUS-DERIVED PEPTIDES CAPABLE OF INDUCING CYTOTOXIC T LYMPHOCYTE RESPONSES
Docket No.:	329368-101A
Art Unit:	1648
Examiner:	Parkin, J.S.

PATENT APPEAL

BOARD OF PATENT APPEALS AND INTERFERENCES:

Enclosed are three copies of the Appeal Brief. Applicants request an oral hearing.

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APPELLANT'S APPEAL BRIEF

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On the Brief

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(1) Real Party in Interest

The inventors have assigned their interest to Scripps Research Institute. Accordingly, Scripps Research Institute is the real party in interest.

(2) Related Appeals and Interferences

On information and belief, there are no other appeals or interferences that will directly affect or have a bearing on the Board's decision in this Appeal.

(3) Status of the Claims

Claims 67-97 are in the application. All other claims have been canceled. All of the pending claims are subject to a rejection under 35 U.S.C. §112, first paragraph. Hence, claims 67-97 are appealed.

(4) Status of Amendments Filed After Final

No amendment has been filed after final. The pending claims are attached as Appendix A. A Submission of Terminal Disclaimer is being filed concurrently with this Appeal Brief to remove a non-appealed issue.

(5) Summary of Invention

The present invention relates to polypeptides that trigger cell-mediated immune responses to hepatitis C virus ("HCV"). Cell-mediated immunity provides a mechanism by which abnormal cells, such as virally infected or cancerous cells, are eliminated. This type of immunity is distinct from antibody-mediated immune responses which are typically directed to infectious agents, rather than to infected host cells. The molecular basis of cell-mediated immunity has been the object of intensive research, which has yielded a wealth of information.

In a virally infected cell, the viral genome directs the synthesis of viral proteins. In a given time period a portion of these viral proteins, along with normal cell products, are

degraded by cellular processes, resulting in fragments that are directed to the cell surface. Appropriate fragments associate with a major histocompatibility complex ("MHC") at the cell-surface. The MHC with bound fragment is available to be bound by a T-cell receptor ("TCR") found on a cytotoxic T-cell (or cytotoxic T lymphocyte, or "CTL"). The process by which T-cells are generated results in an expanded population of T-cells which each have an associated TCR with one of a large repertoire of possible binding specificities. Binding by a given TCR to the MHC-fragment complex can initiate a T-cell response to eliminate an infected cell. Fragments triggering such a response define "cytotoxic T lymphocyte stimulating epitopes." Appropriate polypeptides can be used in conjunction with appropriate antigen presenting cells to stimulate *in vitro* expansion of a patient's CTL precursor cells, thereby increasing the CTLs that can help control an infection.

Applicants tested 53 candidate cytotoxic T lymphocyte stimulating epitopes derived from HCV, and identified the eight reference sequences (of nine to ten amino acids in length) recited in their claims. Applicants recognized that in addition to these sequences, one of ordinary skill applying the testing taught in the specification, and the facile synthesis or biosynthesis taught in the specification and known in the art, could make close analogs of the sequences that retain function. As detailed in other papers in the prosecution of this application, the skill and tools in the art for screening candidate cytotoxic T lymphocyte stimulating epitopes are quite advanced and well adapted to routinely screen, for example, in excess of one thousand (e.g., 1,304) such candidates.

Claim 67 is exemplary:

> 67. An isolated molecule comprising a polypeptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes having a sequence that
>
> (a) has no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding amino acid positions in a CTL epitope which is

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO:3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35), or

(b) has no more than one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26), or

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34),

wherein said molecule comprises at least eight amino acids and less than 50 amino acids, with the provisos that (i) when said selected CTL epitope is SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), then said molecule comprises from at least eight amino acids to less than 25 amino acids, or (ii) when said selected CTL epitope is LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2) then said molecule comprises at most ten amino acids.

(6) Issues

The only issue is whether the claimed invention are properly rejected for a failure of Lilly-type written description.

(7) Grouping of claims

All of the claims below recite aspects of the invention in terms of definite structural boundaries. However, claims 71-74 recite the invention in terms still more definite structural boundaries. Also, claim 97 requires that the polypeptides satisfy two overlapping definitions of definite structural boundaries. Thus, if claim 67 is found to not comprise a failure of Lilly-type written description, all of the claims would similarly be free of such a failure. But,

if claim 67 were found to have such a failure, claims 71-74 and 97 would have to be separately analyzed.

(8) Argument

All of the pending claims, claims 67-97, are asserted to be rejected under 35 U.S.C. §112, first paragraph, with the office action dated May 7, 2003 (the "Office Action") asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time of filing, possessed the invention.

There are two clearly distinct types of rejections for want of written description, as is reviewed in detail in Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319-20, 66 USPQ2d 1429 (Fed. Cir. 2003). Appellant's last response made it clear that detailed support exists for the structural formulas recited in the claims. A review of the Office Action establishes that the asserted failure of written description at issue is of the second type, which is that which was at issue in University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Thus, the focus of this argument will be on the second, Lilly-type of asserted failure of written description.

The type of asserted failure of written description at issue here is quite controversial within the Court of Appeals for the Federal Circuit ("CAFC"). See, Moba, at 1322 et seq., Rader, J., concurring; Enzo Biochem, Inc. v. Gen-Probe Inc., 285 F.3d 1013, 1025 (Fed. Cir. 2002), Dyk, J., dissenting (whether a separate description requirement is appropriate for the field of biotechnology is open to serious question), *opinion of the majority withdrawn* (Enzo I). In Moba, the *per curiam* opinion of the court noted that recent decisions of the CAFC have distinguished Lilly (Moba at 1320), a statement somewhat weaker than, but of the same tenor as, Judge Rader's "Fortunately, the viability of the Lilly rule is on the decline" (Moba at 1326).

Assuming the viability of Lilly, that opinion stated that the written description of a chemical genus "requires a precise definition, such as by structure, *formula* [or] chemical

name." Lilly at 1568, quoting, Friers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601 (Fed. Cir. 1993).[1] Moreover, said the court:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. *Accordingly, such a formula is normally adequate description of the claimed genus.*

Lilly at 1568 (emphasis added). The functional recitations that were disapproved of in Lilly (e.g., "vertebrate cDNA" for proinsulin) are altogether in contrast to a definite formula where one skilled in the art can "visualize or recognize the identity of the members of the genus." Id.

Thus, since the claims here at issue are framed in definite, structural formulas, they simply cannot be brought within the rubric of Lilly. A review of the attached claims will show that they are presented in generic formulae, allowing one skilled in the art to visualize and recognize the identity of the members of the genus. Claim 67, for example, very clearly sets forth *by formula* which polypeptides can and cannot come within the scope of the claims. Such claims are simply not subject to the Lilly-type written description rejection. Accordingly, Appellant submits that the Board should direct that the rejection be withdrawn.

---

[1] This rule, so stated, would appear to be absolute. But, the very author of the Lilly opinion has acknowledged that functional definitions are sometimes acceptable. Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316, 1328, 63 USPQ2d 1609 (Fed. Cir. 2002).

CONCLUSION

For the foregoing reasons, Appellant requests that the rejections under 35 U.S.C. §112 with respect to all of the pending claims, claims 67-97, be reversed and the pending claims in the application allowed.

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Dated: November 7, 2003

APPENDIX A - COPY OF CLAIMS ON APPEAL

67. An isolated molecule comprising a polypeptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes having a sequence that

(a) has no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding amino acid positions in a CTL epitope which is

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO:3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35), or

(b) has no more than one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26), or

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34),

wherein said molecule comprises at least eight amino acids and less than 50 amino acids, with the provisos that (i) when said selected CTL epitope is SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), then said molecule comprises from at least eight amino acids to less than 25 amino acids, or (ii) when said selected CTL epitope is LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2) then said molecule comprises at most ten amino acids.

68. The molecule of claim 67, wherein the isolated peptide has less than 20 amino acids.

69. The molecule of claim 67, wherein the isolated peptide has from 8 to 12 amino acids.

70. The molecule of claim 67, wherein the isolated peptide has 9 or 10 amino acids.

71. The molecule of claim 67, 68, 69, or 70, wherein the isolated molecule has a sequence that has no more than a total of one amino acid substitution, deletion or insertion at the corresponding position as in LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2).

72. The molecule of claim 67, 68, 69, or 70, wherein the isolated molecule has a sequence that has no more than a total of one amino acid substitution, deletion or insertion at the corresponding position as in QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO:3).

73. The molecule of claim 67, 68, 69, or 70, wherein the isolated molecule has a sequence that has no more than a total of one amino acid substitution, deletion or insertion at the corresponding position as in KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28).

74. The molecule of claim 67, 68, 69, or 70, wherein the isolated molecule has a sequence that has no more than a total of one amino acid substitution, deletion or insertion at the corresponding position as in LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35).

75. An immunogenic composition that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes (CTL) comprising molecule which comprises a peptide having a sequence that has no more than a total of a total of two amino acid substitutions, deletions or insertions at the corresponding positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),
LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),
QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO:3),
KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or
LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35) or

has no more than a total of one substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),
SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or

ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42).

76. The immunogenic composition of claim 75, wherein the immunogenic composition further comprises a label selected from the group consisting of a radioactive label, an enzymatic label, and a fluorescent label.

77. The immunogenic composition of claim 75, wherein the immunogenic composition further comprises a solid matrix.

78. The immunogenic composition of claim 75, wherein the immunogenic composition further comprises a carrier molecule.

79. The immunogenic composition of claim 75, wherein the carrier molecule comprises a protein or an immunogenic lipid.

80. The immunogenic composition of claim 75, wherein the immunogenic composition further comprises a T-helper lymphocyte epitope.

81. The immunogenic composition of claim 75, wherein the immunogenic composition further comprises an additional peptide.

82. The immunogenic composition of claim 81, wherein the additional peptide has a sequence that has no more than a total of two amino acid substitutions, deletions or insertions at the corresponding positions as in KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28).

83. A method of stimulating a cytotoxic T-lymphocyte (CTL) response to an hepatitis C viral immunogen, comprising contacting an HLA class I-restricted cytotoxic T lymphocyte with a composition comprising a peptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes comprising a sequence that has no more than a total of two single

amino acid substitutions, deletions or insertions at the corresponding positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO: 3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35) or

has no more than a total of one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or

ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42).

84. The method of claim 83, wherein the contacting occurs in a mammal.

85. The method of claim 83, wherein the mammal is free of HCV disease, is a carrier of HCV, or is afflicted with HCV disease.

86. The method of claim 83, wherein the contacting occurs *in vitro*.

87. The method of claim 83, wherein the peptide comprises the sequence which is ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1).

88. A method of detecting cytotoxic T cells that respond to a T cell epitope of hepatitis C virus (HCV), the method comprising the steps of:

(a) preparing HLA class I-restricted cytotoxic T cells;

(b) preparing HLA class-I matched and -mismatched target cells;

(c) containing separately matched and mismatched target cells with a composition comprising a peptide that induces an HCV-specific response in cytotoxic T lymphocytes having the sequence that has no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO: 3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35) or

has no more than a total of one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or

ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42);

(d) combining the cytotoxic T cells separately with the matched and mismatched target cells; and

(e) measuring cytolysis.

89. The method of claim 88, wherein the cytotoxic T cells are combined with HLA class I-matched lymphocytes.

90. A pharmaceutical composition comprising a peptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes having a sequence that has no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO: 3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35) or

has no more than a total of one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or

ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42), and

a pharmaceutically acceptable carrier.

91. The pharmaceutical composition of claim 90, wherein the peptide has less than 20 amino acids.

92. A conjugate comprising

(a) a molecule, which comprises:

a polypeptide an having no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO: 3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35) or

has no more than a total of one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or

ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42),; and

(b) a substance selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a solid matrix, a carrier and an additional molecule of (a).

93. The conjugate of claim 92, wherein said carrier comprises an immunogenic lipid or protein.

94. A conjugate of claim 92 comprising two molecules, each comprising:

a polypeptide no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO: 3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35) or

has no more than a total of one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26),

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), or

ILDSFDPLV ($NS5_{2252-2260}$; SEQ ID NO:42).

95. The conjugate of claim 94, wherein at least one of said molecules comprises at least eight amino acids and less than 50 amino acids.

96. The conjugate of claim 94, further comprising a T helper epitope.

97. An isolated molecule comprising a polypeptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes having a sequence that has

(a) no more than a total of two single amino acid substitutions, deletions or insertions at the corresponding amino acid positions in a CTL epitope which is

LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2),

QLRRHIDLLV ($E1_{257-266}$; SEQ ID NO:3),

KLVALGINAV ($NS3_{1406-1415}$; SEQ ID NO:28), or

LLFNILGGWV ($NS4_{1807-1816}$; SEQ ID NO:35), or

(b) has no more than one single amino acid substitution, deletion or insertion at the corresponding amino acid positions as in a CTL epitope which is

ADLMGYIPLV ($Core_{131-140}$; SEQ ID NO:1),

LLCPAGHAV ($NS3_{1169-1177}$; SEQ ID NO:26), or

SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34),

wherein said polypeptide comprises at least eight amino acids and less than 50 amino acids, wherein said selected CTL epitope maintains an

`XaaLeuXaaXaaXaaXaaXaaXaaVal` or

`XaaLeuXaaXaaXaaXaaXaaXaaXaaVal` motif,

with the provisos that (a) when said selected CTL epitope is SLMAFTAAV ($NS4_{1789-1797}$; SEQ ID NO:34), then said polypeptide comprises from at least eight amino acids to less than 25 amino acids, and (b) when said selected CTL epitope is LLALLSCLTV ($Core_{178-187}$; SEQ ID NO:2) then said molecule comprises at most ten amino acids.